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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/689,495	10/20/2003	Rui Sousa	310307.90240	4308

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EXAMINER
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KIM, YOUNG J

ART UNIT	PAPER NUMBER
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1637

MAIL DATE	DELIVERY MODE
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05/30/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/689,495	SOUSA, RUI	
	<b>Examiner</b>	<b>Art Unit</b>	
	Young J. Kim	1637	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 06 March 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1,3-5,7-9 and 11-41 is/are pending in the application.
- 4a) Of the above claim(s) 13-24,26,27,29-37,39 and 40 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 1,3-5,11,12,25,28 and 38 is/are allowed.
- 6) ☒ Claim(s) 41 is/are rejected.
- 7) ☒ Claim(s) 7-9 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### DETAILED ACTION

The present Office Action is responsive to the Amendment received on March 6, 2007.

#### *Election/Restrictions*

The instant application contains claims being withdrawn from further consideration as being drawn to non-elected invention without traverse, namely, claims 13-24, 26, 27, 29-37, 39, and 40.

#### *Preliminary Remark*

Claim 41 has been newly submitted.

Claims 1, 3-5, 7-9, 11, 12, 25, 28, 38, and 41 are under prosecution herein as being drawn to the elected invention.

#### *Claim Interpretation*

It is noted that the term, "T7 type RNA polymerase" is specifically defined and thus limited to the following polymerases (section [0068]<sup>1</sup>):

**By "T7-type RNA polymerases" we mean T7, T3,  $\phi$ I,  $\phi$ IIH, W31, ghl, Y, A1122, SP6 and mitochondrial RNAPs.**

#### *Claim Objections – Necessitated by Amendment*

Claims 7-9 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1, which serves as the parent claim for claims 7-9, already defines the double-mutant nucleic acid polymerase as T7 RNA polymerase comprising the mutation

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<sup>1</sup> All references to sections are made with respect to that which was published under pre-grant publication no. 2005/0069907 A1.

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Y639F/H784A. Therefore, claims 7-9, which redefine the polymerase to encompass a broader class of polymerases, fails to further limit the subject matter of a previous claim.

### ***Claim Rejections - 35 USC § 112***

The rejection of claims 10 and 11 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on September 6, 2006, is withdrawn in view of the Amendment received on March 6, 2007.

The scope of enablement rejection of claims 1-12, 25, 28, and 38 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of synthesizing a nucleic acid as claimed, wherein the claims require a T7 RNA polymerase comprising the double mutation, Y639F and H784A, but does not reasonably providing enablement for a method involving any nucleic acid polymerase comprising any double mutations, wherein the mutation results in the reduced discrimination between canonical and non-canonical nucleoside triphosphate, made in the Office Action is withdrawn in view of the Amendment received on March 6, 2007. Specifically, the rejection of claims 2, 6, and 10 are withdrawn in view of their cancellation. The rejection of claims 1, 3-5, 11, 12, 25, 28, and 38 is withdrawn in view of Applicants' amendment received on March 6, 2007, amending the claims to the enabled scope. The rejection of claims 7-9 is withdrawn in view of their objection for failure to further limit the parent claim (as discussed above).

### ***Rejection, New Grounds, Necessitated by Amendment***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claims 41 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of synthesizing a nucleic acid as claimed, wherein the claims require a T7 RNA polymerase comprising the double mutation, Y639F and H784A, does not reasonably provide enablement for a method involving T7 RNA polymerase comprising any double mutations; or method involving SP6 or T3 RNA polymerase, wherein said double mutation results in the reduced discrimination between canonical and non-canonical nucleoside triphosphate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation are summarized in *In Re Wands* (858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). They include (A) the quantity of experimentation necessary, (B) the amount of direction or guidance presented, (C) the presence or absence of working examples, (D) the nature of the invention, (E) the state of the prior art, (F) the relative skill of those in the art, (G) the predictability or unpredictability of the art, and (H) the breadth of the claims.

#### Breadth of the claims

Claim is drawn to a method which involve the use of a T7 RNA polymerases comprising any double mutation; or T3 or SP6 (claims 7-9), each of these polymerases comprising any double mutation, wherein said double mutation results in the reduced discrimination between canonical and non-canonical nucleotide triphosphates.

#### Amount of Guidance:

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The instant specification disclose and guides a skilled artisan in that in T7 RNA polymerase, the conservative mutation at tyrosine at position 639, and at histidine at position 784 (section [0026]).

On section [0081], Applicants state that the know mutation produced at the position 639 of the T7 RNA polymerase (from tyrosine to phenylalanine) does not overcome the barrier to synthesis of nucleic acid by incorporation of non-canonical nucleoside triphosphates which have bulkier substituents at the 2'-positions.

On section [0082], Applicants state that addition of a second mutation produced on the Y639F T7 RNA mutant polymerase, wherein the second mutation is produced at position 784 (from histidine to alanine) made room enough for the incorporation of non-canonical nucleoside triphosphates having bulkier substituents at the 2'-position.

The instant specification discloses that the amino acid in position Y631 of wild type SP6 RNAP corresponds to the Y639 site in T7 RNAP, and that mutagenesis of this site resulted in a Y631F mutant SP6 RNAP which, "has a similar reduced discrimination for dNTPs compared to rNTPs like the Y639 mutant T7 RNAP (section [0169]).

With regard to the characterization of T3 RNA polymerase, the specification merely evidences that position Y573F mutation also produces the characteristic of the mutant polymerase being able to utilize 2'-NH<sub>2</sub> and 2'-F NTP (non-canonical nucleotide triphosphates) as substrates (section [0078]).

Hence, the specification gives guidance for a single member of polymerase, in addition to T7 RNA polymerase; a SP6 polymerase having a particular mutation at the position 631; and a T3 RNA polymerase having a particular mutation at the position 573, which resulted in the reduce discrimination.

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In addition, it should be brought to the attention that the claims are drawn to using a double mutant polymerase, wherein the claims are not limited to any particular mutations.

The specification contemplates a single, second mutation on T7 RNA polymerase, said second mutation being made at position H784 of T7 RNA polymerase (section [0175]).

While the specification makes a prophetic statement that second mutations could be produced at a corresponding positions on T7-like [*sic*] RNAPs, particularly, positions H779 of SP6 RNAP, or H785 of T3 RNAP, which would produce the equal effects, the specification is absolutely silent on whether such mutants were produced or whether the mutants exhibited the asserted effects. Only a particular mutant of T7 RNA polymerase, Y639F/H785 doublet mutant T7 RNA polymerase was disclosed as having enhanced reduced discrimination between canonical and non-canonical nucleoside triphosphates.

#### Absence of working example

The instant specification absolutely lacks any working examples for SP6 and T3 RNA polymerase, but rather only the single double mutant, Y639F/H784 T7 RNA polymerase

The examiner does note that specification does appear to give some evidence that a single mutation produced in SP6 polymerase, wherein the mutation is Y631F; and a single mutation produced in T3 RNA polymerase, wherein the mutation is Y573F, resulted in the incorporation of 2'-NH<sub>2</sub> and 2'-F NTP (non-canonical nucleoside triphosphate) (see section [0078]).

The examiner also notes that section [0175] provides the assertion that the second mutation at the position H779 of SP6 polymerase, and at the position H785 of T3 RNA polymerase, with the particular mutation to the residue Alanine (section [0176]).

However, as Applicants' own publication states the introduction of such second mutation may not result in a functional enzyme:

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“Since the Y639F mutation specifically eliminates discrimination of the ribose 2'-group character, it is less useful for incorporating substrates modified at other positions...However, the active site of T7 RNAP has been heavily mutagenized...A caveat is that these mutations **tend to reduce activity and any gain in the reduced substrate specificity may not compensate for the lower activity.**” (page 1563, 2<sup>nd</sup> column, 2<sup>nd</sup> paragraph).

Hence, Applicants are invited to provide evidence to this assertion that the occurrence of said second mutation does, in fact, result in the reduced discrimination characteristic in SP6 and T3 RNA polymerase for facilitated prosecution.

The instant specification also does not disclose a reasonable number of species embraced by the sub-genus genus claim pertaining to double mutants comprising any mutations

Nature of invention:

The nature of invention relates to the complex nature of proteins, correlating their structure with functions, and altering the functions via mutagenesis.

Unpredictability:

It is well established in the art that the function of the protein is intimately related to its structure. As already discussed, it remains largely unpredictable for a skilled artisan to employ a large genus embracing any double-mutations from T7 RNA polymerase, SP6 polymerase and T3 RNA polymerase, without the disruption of the function of the protein.

The unpredictability is also demonstrated by Applicants' own specification.

On section [0134], Applicants experiment with different types of mutation produced at the position 639 of the T7 RNA polymerase. It should be noted that a single mutation produced at position 639 of T7 RNA polymerase, having a particular mutation from tyrosine (Y) to phenylalanine



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(F) resulted in the reduced discrimination between canonical and non-canonical nucleoside triphosphate.

However, as disclosed in Table III, when tyrosine at the same position was mutated to a serine (S), the discriminating ability of the mutant polymerase is similar to the wild type T7 RNA polymerase.

In addition, mutant G640A, which contains a mutation adjacent to the position found to be critical in producing the reduced discrimination did “not affect substrate discrimination.” [0134].

Clearly, the unpredictability in protein modification for producing polymerases with desired activity is very high.

State of Prior Art:

Applicants appear to have publication drawn to the single identified double mutant T7 RNA polymerase comprising mutations Y639F/H784A, the same single double mutant disclosed in the instant specification (Nucleic Acids Research, December 2002, vol. 30, no. 24, e138).

Skill Level & Conclusion:

While the skill level of the practitioner is deemed high, given the complex nature of the protein function, one of skill in the art would not be able to practice the invention commensurate in scope of the claims without undue experimentation based on the lack of guidance of the instant specification, absence of working examples for a reasonable number of species embraced within the genus and subgenus, and highly unpredictable and complex nature of protein functions.

Response to Arguments:

Applicants state that Applicants do not agree with the Office’s characterization of the specification in that other members of T7-like polymerases are not enabled (page 12, Response).

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As already discussed above, it is respectfully submitted it would require an undue amount of experimentation to practice the invention fully commensurate in scope of the instant claim.

### ***Claim Rejections - 35 USC § 102***

The rejection of claims 1, 3, and 5-12 under 35 U.S.C. 102(a) as being anticipated by Padilla et al. (Nucleic Acids Research, December 2002, vol. 30, no. 24, e138, pages 1-4), made in the Office Action mailed on September 6, 2006 is withdrawn in view of the arguments presented in the Amendment received on March 6, 2007.

The examiner acknowledges that the denial of priority to U.S. provisional application, serial number, 60/420,009, was erroneous. Based on this fact, Padilla et al. is no longer prior art.

### ***Conclusion***

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

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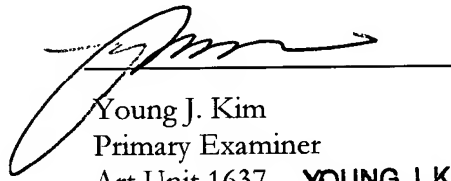
calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

### *Inquiries*

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m (M-W and F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

  
Young J. Kim  
Primary Examiner  
Art Unit 1637  
5/28/2007 **YOUNG J. KIM**  
**PRIMARY EXAMINER**

YJK